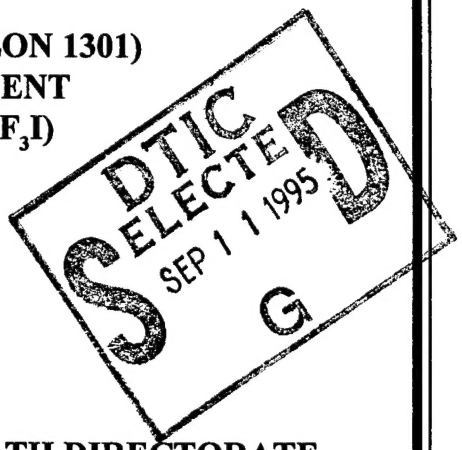
AL/OE-TR-1994-0068

GAS UPTAKE KINETICS OF BROMOTRIFLUOROMETHANE (HALON 1301) AND ITS PROPOSED REPLACEMENT IODOTRIFLUOROMETHANE (CF_3I)



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January 1994

FINAL REPORT FOR THE PERIOD JUNE THROUGH DECEMBER 1993

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TECHNICAL REVIEW AND APPROVAL

AL/OE-TR-1994-0068

The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

Terry A. Childress

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave Blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	January 1994	Final - June-December 1993

4. TITLE AND SUBTITLE
Gas Uptake Kinetics of Bromotrifluoromethane (Halon 1301) and Its Proposed Replacement Iodotrifluoromethane (CF_3I)

5. FUNDING NUMBERS
Contract F33615-90-C-0532
PE 62202F
PR 6302
TA 630200
WU 63020002

6. AUTHOR(S)
R.J. Williams, A. Vinegar, J.Z. Byczkowski, J.R. Creech, R.K. Black, S.K. Neurath, and G.W. Jepson

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
ManTech Environmental Technology, Inc.
Toxic Hazards Research Unit
P.O. Box 31009
Dayton, OH 45437-0009

8. PERFORMING ORGANIZATION REPORT NUMBER
4300-9306

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Armstrong Laboratory, Occupational and Environmental Health Directorate
Toxicology Division, Human Systems Center
Air Force Materiel Command
Wright-Patterson AFB OH 45433-7400

10. SPONSORING;MONITORING AGENCY REPORT NUMBER
AL/OE-TR-1994-0068

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

A physiologically based simulation approach was used to estimate *in vivo* metabolic constants in male Fischer 344 rats for the two chemicals, bromotrifluoromethane (Halon 1301), and its proposed replacement candidate, iodotrifluoromethane (CF_3I). A closed recirculating exposure system was used to collect a series of gas uptake curves for both chemicals at equivalent initial exposure concentrations. Additionally, tissue:air partition coefficients were determined experimentally for each chemical and incorporated into a physiologically based pharmacokinetic model, which was then used to simulate the uptake of the chemicals. By iteratively adjusting the constants describing metabolism of the chemical, and optimized fit of the series of uptake curves was obtained for each chemical. This simulation approach adequately described the overall uptake of each chemical from the chamber. Given the relatively low level of partitioning of these chemicals into tissues and their relative inertness, this approach could not be used with certainty to discriminate between metabolism by saturable and/or first-order process and no metabolism at all.

14. SUBJECT TERMS
Gas Uptake Kinetics
Bromotrifluoromethane
Halon 1301
CF_3I
Physiologically Based Pharmacokinetic Model
Iodotrifluoromethane

15. NUMBER OF PAGES
36

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED	UL

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

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PREFACE

The research reported herein was conducted by the Toxic Hazards Research Unit, ManTech Environmental Technology, Inc., and serves as a final report for the determination of the gas uptake kinetics of bromotrifluoromethane (Halon 1301) and its proposed replacement iodotrifluoromethane (CF_3I). The research described in this report began in June 1993 and was completed in December 1993. It was performed under Department of the Air Force Contract No. F33615-90-C-0532 (Study No. F21). Lt Col James N. McDougal and Lt Col Terry A. Childress served as Contract Technical Monitor, respectively, for the Toxicology Division, Occupational and Environmental Health Directorate, Armstrong Laboratory, Wright-Patterson Air Force Base, OH.

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ABBREVIATIONS

°C	Degrees celsius
Halon 1301	Bromotrifluoromethane
F-344	Fischer 344 (rats)
FID	Flame ionization detector
g	Gram
GC	Gas chromatograph(y)
h	Hour
L	Liter
m	Meter
min	Minute
mL	Milliliter
BW	Body weight
GI	Gastrointestinal
mm	Millimeter
PBPK	Physiologically based pharmacokinetic
ppm	Parts per million
CF_3I	Iodotrifluoromethane

SECTION 1
INTRODUCTION

The aim of this study was to measure tissue:air partition coefficients and to describe the kinetics of bromotrifluoromethane (Halon 1301) and its proposed replacement chemical, iodotrifluoromethane (CF_3I), via recirculating gas uptake exposure methods.

Inhalation pharmacokinetics for both chemicals were determined experimentally in Fischer 344 (F-344) male rats. A physiologically based pharmacokinetic (PBPK) model was used to describe mathematically the disposition and metabolism of both chemicals employing chemical-specific parameters and apparent whole-body metabolic constants calculated from these experiments.

Given the relatively low level of partitioning of these chemicals into tissues and their relative inertness, this approach could not be used with certainty to discriminate between metabolism by saturable and/or a first-order process and no metabolism at all.

SECTION 2
MATERIALS AND METHODS

TEST CHEMICALS

Bromotrifluoromethane (Halon 1301):

Trade name	FC-13B1
CAS #	75-63-8
Mol. Weight	148.91
Empirical formula	CF_3Br
Boiling point (°C)	-57.8

Iodotrifluoromethane (CF_3I):

Trade name	Trifluoromethyl iodide
CAS #	2314-97-8
Mol. Weight	195.9
Empirical formula	CF_3I
Boiling point (°C)	-22.5

The 1301 and CF_3I from PCR Inc. (Gainesville, FL) were used in this study.

ANIMALS

Male F-344 (200 to 350 g) rats (*Rattus norvegicus*) were obtained from Charles River Breeding Laboratories (Kingston, NY). Animals received Purina Formulab #5008 and softened water *ad libitum*. They were housed in plastic cages (2 to 3/cage) with hardwood chip bedding prior to exposure and were maintained on a 12-h light/12-h dark light cycle at constant temperature (22 ± 1 °C) and humidity (40 to 60%). Cages were changed twice per week. Animals were marked for identification with a tail tattoo.

The animals used in this study were handled in accordance with the principles stated in the *Guide for the Care and Use of Laboratory Animals*, prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, Department of Human and Health Services, National Institute of Health Publication #86-23, 1985, and the Animal Welfare Act of 1966, as amended.

DETERMINATION OF PARTITION COEFFICIENTS

Partition coefficients were determined by using a modified version of the vial-equilibration technique described by Gargas et al. (1989). Whole tissue was harvested and minced into a tissue slurry versus prepared as a tissue homogenate in saline. Rats used to determine partition coefficients were euthanatized with CO_2. Blood was collected from the posterior *vena cava* using a heparinized syringe. Liver (L), muscle (M, quadriceps), fat (F, epididymal and perirenal), and gastrointestinal tract (G, stomach and small intestine) also were removed for analysis. Blood samples (1.0 mL) were placed in 12.4 mL glass vials and incubated/mixed for 3 h at 37 °C with 800 ppm of chemical in the vial headspace. Incubation time was determined by initially exposing samples for 1, 3, 5, or 7 h and observing that no change was seen after 3 h. Chemical concentration was determined by initially using 100, 400, or 800 ppm and observing no difference between 400 and 800 ppm. Whole tissue samples (1.0 g of L and M; 0.50 g of F and G) were minced and incubated/mixed under the same conditions as for blood, except fat was equilibrated for 5 to 8 h.

The chemical concentrations in the headspace were analyzed using a HP19395A headspace sampler (Hewlett-Packard, Avondale, PA) connected to a HP5890 gas chromatograph (GC) (Hewlett-Packard, Palo Alto, CA) equipped with a hydrogen flame ionization detector (FID). Column selection and GC conditions varied for each chemical. For Halon 1301, a 25 m x 0.53 mm Chromopack PoraplotQ (Plot Fused Silica) column was used. Gas chromatography conditions were set with the detector temperature at 250 °C, injection temperature 125 °C, helium carrier gas at 13.0 mL/min column flow plus 13.0 mL/min make-up flow, and oven temperature held constant at 70 °C. For CF_3I, a 12" x 1/8" stainless steel 10% SE-30, WHP 80/100 Chromosorb column was used. Gas chromatography conditions were set with the detector temperature at 250 °C, injection temperature 125 °C, nitrogen carrier gas flow at 30.0 mL/min, and oven temperature held constant at 60 °C.

GAS UPTAKE AND METABOLIC CONSTANTS

A closed chamber recirculating gas uptake system with a volume of 8.0 L was used for the estimation of whole animal metabolic constants (V_{max}, K_m, and K_f). Three F-344 rats were exposed to each study chemical using a closed recirculating gas uptake system similar to that described by Gargas et al. (1986). Four to five exposure concentrations were performed for 6 h each (Halon 1301 concentrations were 122, 1202, 2993, and 5557 ppm; and CF_3I concentrations were 112, 648, 1228, 2715, and 5867 ppm). Ascarite (150 g) was used as the CO_2 absorber. Oxygen concentrations were maintained at (21% ± 1) during the exposures. The system flow was maintained at 2.1 L/min with the flow to the sample loop of the GC at 100 mL/min.

The chemical concentrations in the chamber atmosphere were monitored every 5 min for the first 30 min and every 15 min thereafter, using a gas sampling valve connected to a HP5890 GC.

Chromatography was performed on a 25 m x 0.53 mm Chromopack Poraplot Q (Plot Fused Silica) column. The GC was equipped with a hydrogen FID with temperature set at 250 °C, helium carrier flow at 12.1 mL/min with make-up flow of 14.2 mL/min, injection temperature of 125 °C for Halon 1301 and 150 °C for CF_3I, and oven temperature held constant at 80 °C for 1301 and 125 °C for CF_3I.

MODEL DEVELOPMENT

SIMUSOLV (DOW Chemical Co., Midland, MI), a Fortran-based continuous simulation language with optimization capabilities, was used on a VAX/VMS 8530 mainframe computer (Digital Equipment Corp., Maynard, MA). The general form of the PBPK model (Figure 1) followed that of Ramsey and Andersen (1984). The codes that made up the PBPK models are given in the Appendices. Parameters were optimized by SIMUSOLV which is using the log likelihood function as the criterion and either the generalized reduced gradient method for single parameter optimization or the Nelder-Mead search method for multiple parameters optimization to adjust the values.

Physiological constants for calculating volumes of the compartments are shown in Table 1. Tissue volume constants are scaled to the actual body weight (BW) of the rats under study (fat volume was derived from Anderson et al. [1993]); other constants were according to Linstedt (Physiological Parameters Working Group, ILSI Risk Science Institute, unpublished data). Blood flows are expressed as a percentage of cardiac output which was scaled to BW to the exponent 0.75. Alveolar ventilation is also scaled to BW to the exponent 0.75. Cardiac output and alveolar ventilation, based on those described by Gargas et al. (1986) for resting animals, are summarized in Table 1.

Blood:air and tissue:air partition coefficients were obtained as described above. Metabolic constants were determined using the model to obtain a simultaneous fit to the closed chamber gas uptake data. The constants are scaled to BW using the allometric relationship described by Andersen et al. (1987).

TABLE 1. KINETIC CONSTANTS AND PHYSIOLOGICAL PARAMETERS USED IN PBPK MODELING IN RATS

Description	[Units] Parameter
Tissue Volumes	[Fraction of Body Weight:BW]
Liver	$V_LC = 0.037$
Fat	$V_FC = 0.01*(35*BW+2.1)$
GI Tract	$V_GC = 0.033$
Slowly Perfused	$V_SC = 0.558$
Rapidly Perfused	$V_RC = 0.031$
Flow Rates	[L/h/kg]
Alveolar Ventilation	$Q_PC = 14.0$
Cardiac Output	$Q_CC = 14.0$
	[Fraction of Cardiac Output]
Liver	$Q_LC = 0.032$
Fat	$Q_FC = 0.058$
GI Tract	$Q_GC = 0.183$
Slowly Perfused	$Q_SC = 0.255$
Rapidly Perfused	$Q_RC = 0.472$

PBPK MODEL CONSTRUCTION

Figure 1 shows the scheme of the PBPK model, essentially as described by Ramsey and Andersen (1984). An additional compartment was added to describe the gastrointestinal (GI) tract.

Mass transfer differential equations describing each compartment of the PBPK model for both chemicals (schematically shown in Figure 1) are presented below.

For simple, well-stirred compartments in which neither metabolism or other losses occurred (rapidly and slowly perfused tissues, fat, and gut), the change in the amount of chemical (A_i) over time (t) was described as follows:

$$dA_i/dt = Q_i(CA - CV_i)$$

where subscript $_i$ represents "i-th" compartment; Q_i represents the blood flow through the "i-th" compartment; CA represents the arterial concentration; CV_i represents the venous concentration leaving the "i-th" compartment ($CV_i = C_i/P_i$; where C_i is a concentration in the tissue in "i-th" compartment and P_i is the tissue/blood partition coefficient for "i-th" compartment. $C_i = A_i/V_i$, where V_i represents the volume of the "i-th" compartment).

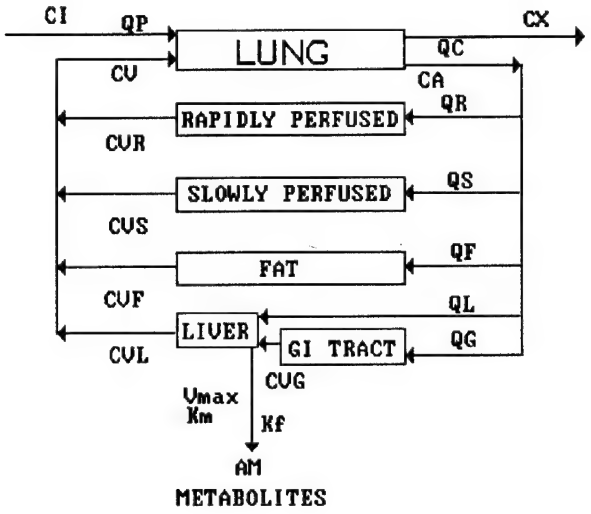

Figure 1. A scheme of PBPK model used for computer simulations of Halon 1301 and CF_3I disposition and metabolism in rats.

For the liver compartment, a loss term (RAM) was added to the well-stirred compartment description to account for rate of metabolism ($RAM = V_{max}CV_L/(K_m + CV_L) + K_fCV_LV_L$; where V_{max} is apparent-maximal velocity rate of the metabolism, CV_L is venous concentration leaving the liver, K_m is apparent Michaelis-Menten constant, K_f is the first order rate of metabolism, and V_L is the volume of liver):

$$dA_L/dt = Q_L(CA - CV_L) + Q_G(CV_G - CV_L) - RAM$$

where Q_G is the blood flow through the portal circulation (from the GI tract) and CV_G is a concentration of the chemical that reaches liver via portal circulation (from the GI tract). Units for the above variables are as follows: amounts - mg, concentrations - mg/L, flows - L/h, and rates - mg/h. The actual codes used for computer simulation of Halon 1301 are included in APPENDIX A, and codes used for computer simulation of CF_3I are included in APPENDIX B.

SECTION 3
RESULTS

PARTITION COEFFICIENTS

The rat tissue:air partition coefficients determined for Halon 1301 and CF_3I, which were used in the PBPK model optimization, are shown in Table 2.

TABLE 2. PARTITION COEFFICIENTS FOR HALON 1301 AND CF_3I IN RATS

Partition Coefficients		Ratio ± S.D. Halon 1301 (n=32)	CF3I (n=10)
Blood:air	PB	0.72 ± 0.48	1.75 ± 0.35
Liver:air	PLA	0.85 ± 0.58	1.22 ± 0.22
Fat:air	PFA	3.95 ± 2.91	11.24 ± 1.75
Gut:air	PGA	0.69 ± 0.51	1.57 ± 0.66
Rapidly perfused/air	PRA	0.85 ± 0.58	1.22 ± 0.22
Slowly perfused/air	PSA	0.59 ± 0.40	1.27 ± 0.30

GAS UPTAKE STUDIES

The inhalational uptake of both Halon 1301 and CF_3I by the rat showed two discernable phases: a rapid equilibration phase that lasted up to 60 min followed by a slow linear uptake phase (Figures 2 through 5). Uptake of Halon 1301 (Figure 2) was simulated without the necessity of attributing any metabolic capacity by the rats. Simulation of the uptake of CF_3I (Figures 3 through 5) required some attribution of metabolic capacity by the rats. Attribution of both saturable (Vmaxc=0.375, Km=0.1) and first order (Kfc=1.6) metabolism and a chamber loss of 2.7% is shown compared to no metabolism with the same chamber loss rate (Figure 3). The upper curve with each set of data represents the no metabolism condition. Attribution of saturable (Vmaxc=0.375, Km=0.1) metabolism alone and a chamber loss of 4.0% is shown compared to no metabolism with a chamber loss of 2.7% (Figure 4). Again the upper curve with each set of data represents the no metabolism condition. The two sets of simulations with attributed metabolism shown in Figures 3 and 4 are shown compared in Figure 5 indicating virtual overlap, indicating a lack of discrimination between first order metabolism and chamber loss. The constants and rates used for each of the preceding simulations are summarized in Table 3.

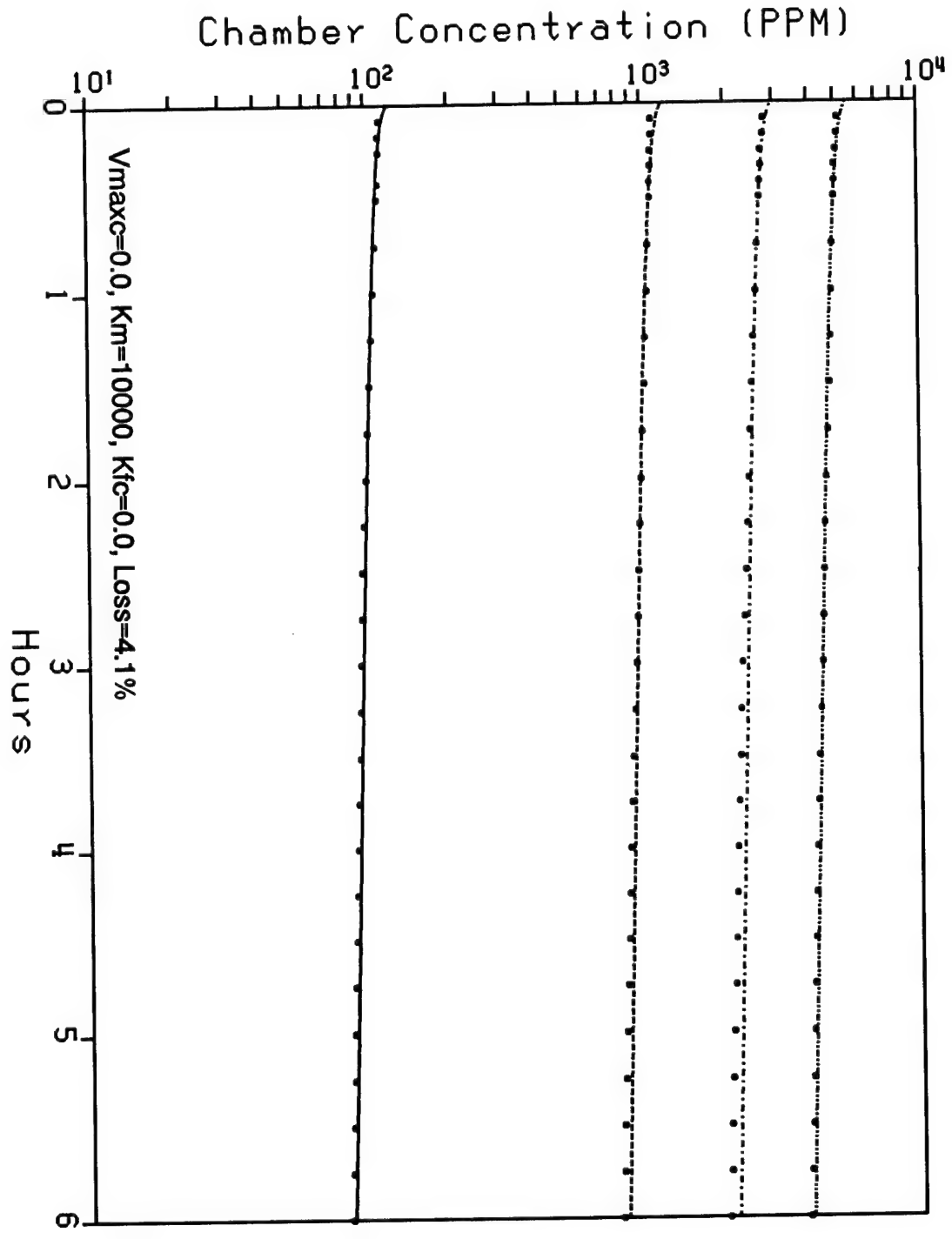

Figure 2. Halon 1301 Gas Uptake.

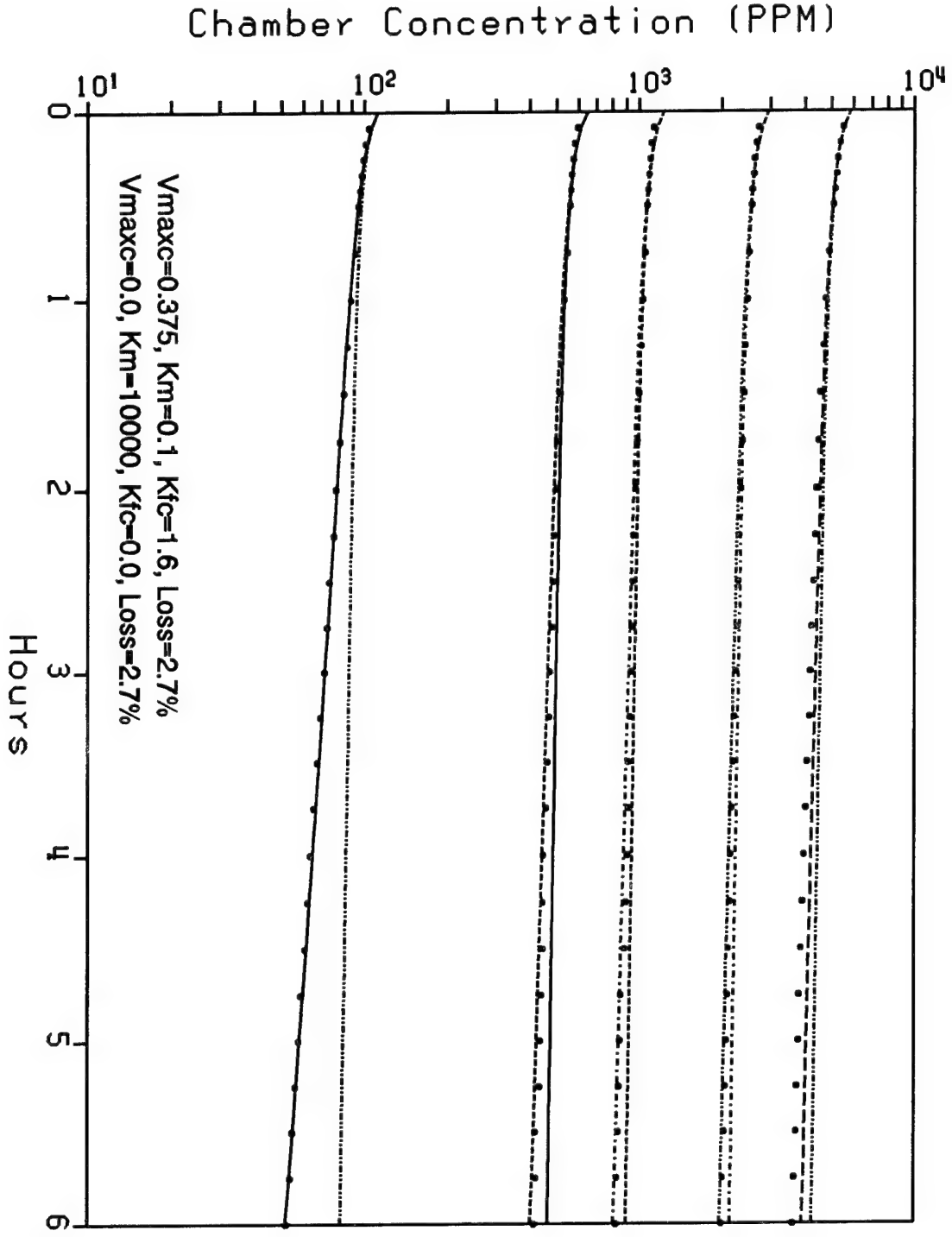

Figure 3. CF_3I Gas Uptake – Comparison of Metabolism and No Metabolism with Same Loss Rate.

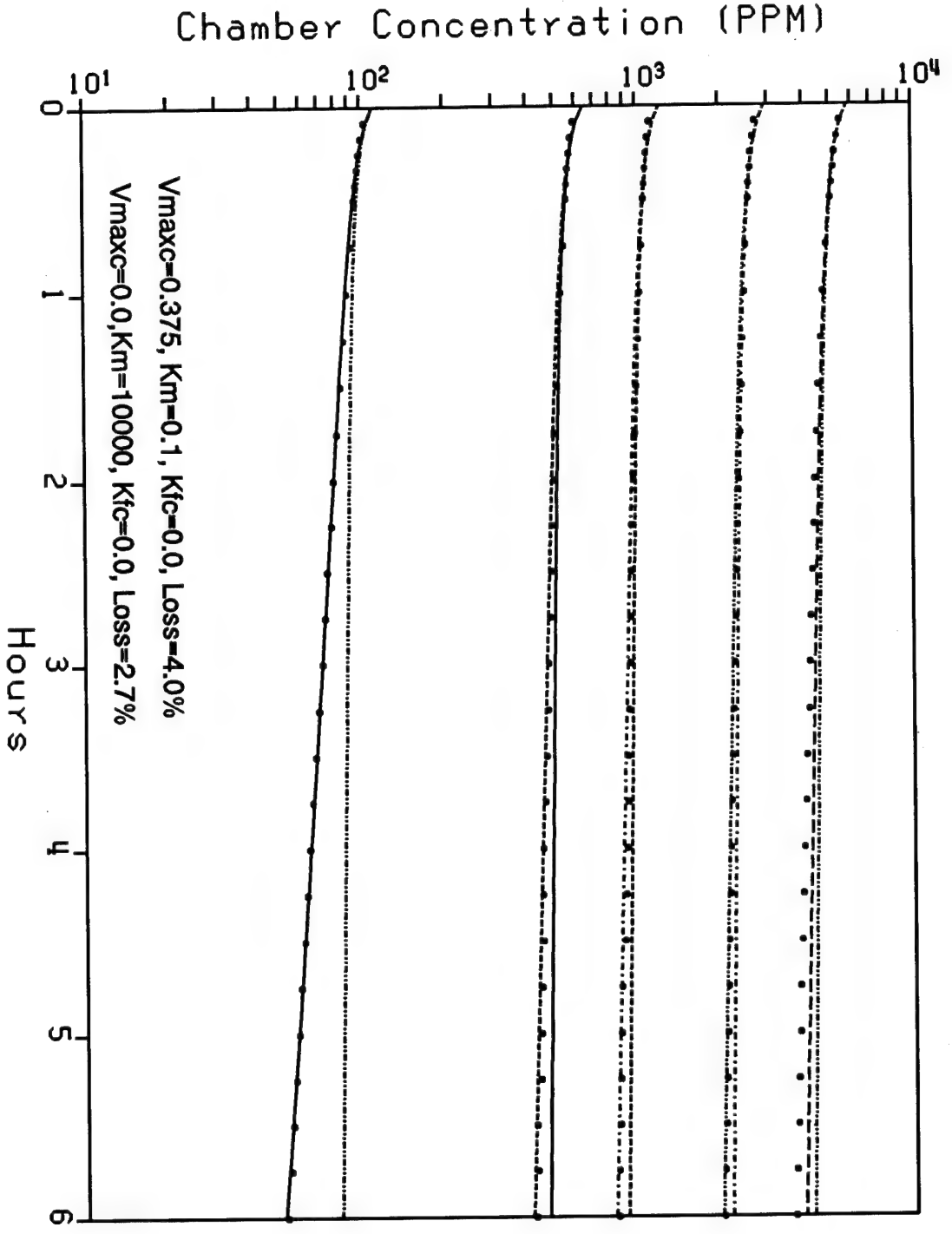

Figure 4. **CF_3I Gas Uptake – Comparison of Metabolism and No Metabolism with Different Loss Rate.**

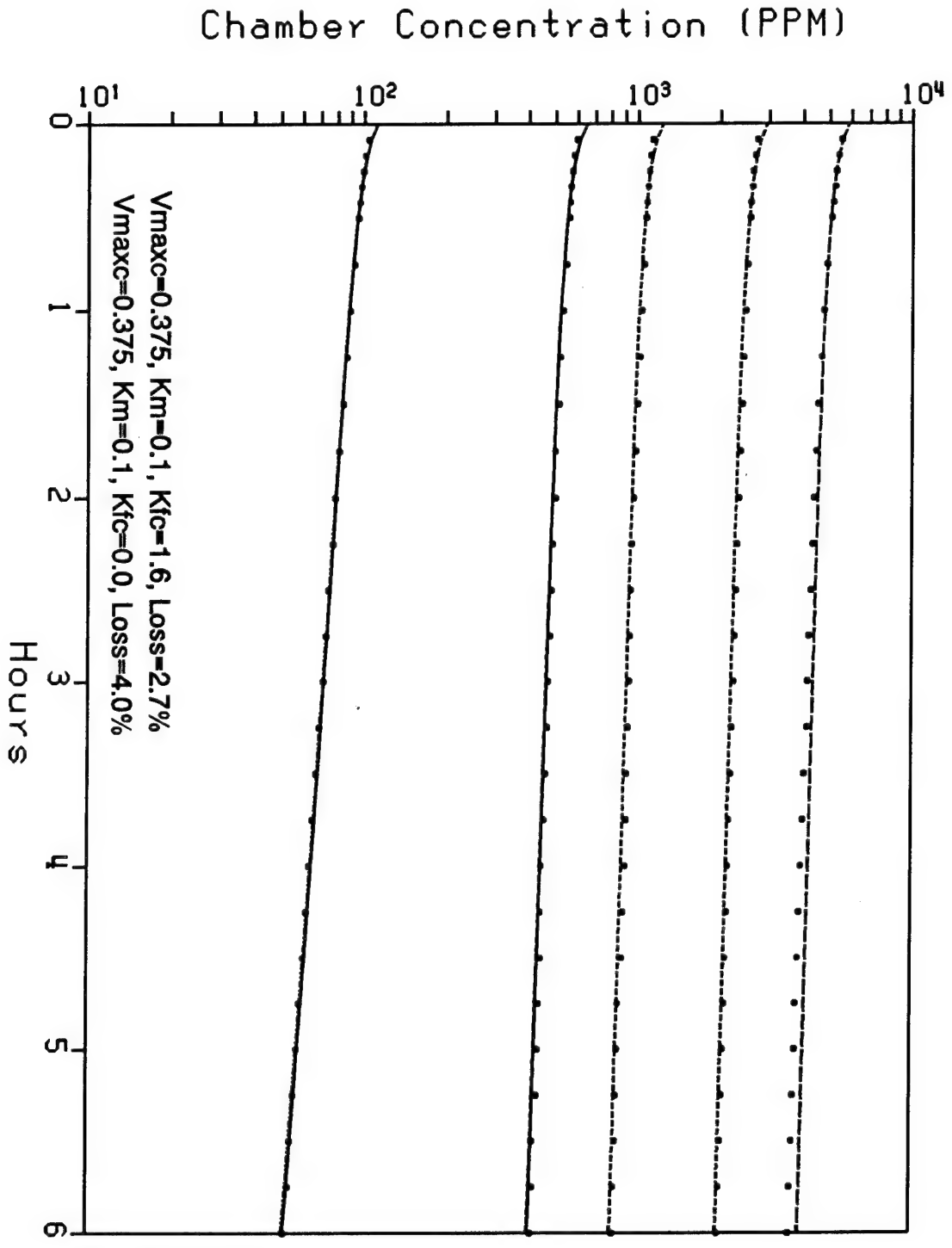

Figure 5. CF_3I Gas Uptake – Comparison of Saturable and First-Order Metabolism with Saturable Metabolism Alone, Each Having Different Loss Rates

TABLE 3. SUMMARY OF METABOLIC CONSTANTS AND CHAMBER LOSS RATES USED IN SIMULATING UPTAKE OF HALON 1301 AND CF_3I BY RATS

Figure	Chemical	Vmaxc mg/h/kg	Km mg/L	Kfc 1/h/kg	Chamber Loss
2	Halon 1301	0.0	10000	0.0	4.1%
3	CF_3I	0.375	0.1	1.6	2.7%
	CF_3I	0.0	10000	0.0	2.7%
4	CF_3I	0.375	0.1	0.0	4.0%
	CF_3I	0.0	10000	0.0	2.7%
5	CF_3I	0.375	0.1	1.6	2.7%
	CF_3I	0.375	0.1	0.0	4.0%

SECTION 4
DISCUSSION

This simulation approach for analysis of gas uptake data has been shown to distinguish between single and multiple metabolic pathways of several previously studied dihalomethanes and numerous other volatile organic compounds. Halon 1301 gas uptake data were simulated successfully by assuming that no metabolism of the chemical was occurring and that after initial uptake by the animal further losses were those occurring in the uptake system itself. Simulation of the CF_3I required some attribution of metabolism by the rats beyond losses to the system. Another indication that chemical was disappearing beyond that taken up by the chamber is demonstrated by the chromatograms of the chamber air. As gas uptake experiments progressed, a second peak besides that for the parent chemical appeared and increased in size. This could represent a metabolite resulting from the metabolism of the chemical by the rats or could represent a product resulting from spontaneous breakdown of CF_3I in the chamber. The product appeared only when live rats were in the chamber with the parent chemical. However, further experiments would be necessary to determine the identity and origin of the second chromatographic peak.

SECTION 5

CONCLUSIONS

1. The PBPK model adequately describes the disappearance of both chemicals from the chamber atmosphere during gas uptake experiments.

2. Both chemicals had low solubility (partition) in blood and tissues and had minimal, if any, enzymatic metabolism in rats.

3. Further experiments are necessary to determine the identity and origin of the second peak seen during the uptake of CF_3I.

SECTION 6

REFERENCES

Anderson, Y.B., J.A. Jackson, and L.S. Birnbaum. 1993. Maturational changes in dermal absorption of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in Fischer 344 rats. *Toxicol. Appl. Pharmacol.* 119:214-220.

Andersen, M.E., H.J. Clewell, M.L. Gargas, F.A. Smith, and R.H. Reitz. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. *Toxicol. Appl. Pharmacol.* 87:185-205.

Gargas, M.L., M.E. Andersen, and H.J. Clewell III. 1986. A physiologically based simulation approach for determining metabolic constants from gas uptake data. *Toxicol. Appl. Pharmacol.* 86:341-352.

Gargas, M.L., R.J. Burgess, D.E. Voisard, G.H. Cason, and M.E. Andersen. 1989. Partition coefficients of low-molecular weight volatile chemicals in various liquids and tissues. *Toxicol. Appl. Pharmacol.* 98:87-99.

Ramsey, J.C. and M.E. Andersen. 1984. A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. *Toxicol. Appl. Pharmacol.* 73:159-175.

APPENDIX A

CODES AND COMMAND FILE FOR COMPUTER SIMULATION OF HALON 1301 PHARMACOKINETICS

```
PROGRAM: CLOSED CHAMBER MODEL 1301 GAS-UPTAKE EXPOSURES
'Based on:'
'Template Model with Code for Gut and Liver - 30 March 1993'
'-----------------------------------------------------------------'
INTEGER  J
ARRAY CONCJ(4), BWJ(4)
CONSTANT CONCJ = 121.5,1201.5,2992.5,5557.
CONSTANT BWJ = .307,.326,.310,.311
CONSTANT J=1, JJ=1.0

INITIAL

ALGORITHM IALG = 2  $'Gear method for stiff systems'

     'Timing commands'

CONSTANT   TSTOP = 6.   $'Length of experiment (hrs)'
CONSTANT    CINT = .05  $'Communication interval'

J = INT(JJ)
CONC = CONCJ(J)
BW = BWJ(J)
CONSTANT   KL  = .041   $'FIRST ORDER CHAMBER LOSS (LN AREA CTS/HR)'
CONSTANT   BW = 0.31   $'Body weight (kg)'

CONSTANT   QPC = 14.00   $'Alveolar ventilation rate (l/hr)'
CONSTANT   QCC = 14.00   $'Cardiac output (l/hr)'

CONSTANT   QLC = .032  $'Fractional blood flow to liver'
CONSTANT   QGC = .183  $'Fractional blood flow to gut'
CONSTANT   QFC = .058  $'Fractional blood flow to fat'
CONSTANT   QSC = .255  $'Fractional blood flow to slow'
CONSTANT   QRC = .472  $'Fractional blood flow to rapid'

CONSTANT   VLC = .037  $'Fraction liver tissue'
CONSTANT   VGC = .033  $'Fraction gut tissue'
CONSTANT   VSC = .558  $'Fraction slow tissue'
CONSTANT   VRC = .031  $'Fraction rapid tissue'

VFC = .01*(35.0*BW+2.1)  $'Fraction fat tissue'

CONSTANT   PLA = 0.85  $'Liver/air partition coefficient'
CONSTANT   PGA = 0.69  $'Gut/air partition coefficient'
CONSTANT   PFA = 3.95  $'Fat/air partition coefficient'
CONSTANT   PSA = 0.59  $'Slowly perfused tissue/air partition'
CONSTANT   PRA = 0.85  $'Rapidly perfused tissue/air partition'
CONSTANT   PB =  0.715 $'Blood/air partition coefficient'

PL=PLA/PB  $'Liver/blood partition coefficient'
PG=PGA/PB  $'Gut/blood partition coefficient'
PF=PFA/PB  $'Fat/blood partition coefficient'
PS=PSA/PB  $'Slow/blood partition coefficient'
PR=PRA/PB  $'Rapid/blood partition coefficient'

CONSTANT   MW = 148.91 $'Molecular weight (g/mol)'
CONSTANT   VMAXC=0.0   $'Maximum velocity of metabolism (mg/hr-1kg)'
CONSTANT   KM   =10000  $'Michaelis-Menten constant (mg/l)'
CONSTANT   KFC  =0.0    $'First order metabolism rate constant (/hr-1kg)'
CONSTANT   CONC =100.  $'Inhaled concentration (ppm)'
CONSTANT   RATS = 3.   $'Number of rats (for closed chamber)'
CONSTANT   VCHC = 8.   $'Volume of closed chamber (l)'
CONSTANT   SODA = .15  $'Volume of soda lime (l)'
```

```
VCH = VCHC-(RATS*BW)-SODA    $'Net chamber volume (l)'
AI0 = CONC*VCH*MW/24450.     $'Initial amount in chamber (mg)'

     'Scaled parameters'

       QC = QCC*BW**0.75
       QP = QPC*BW**0.75
       QL = QLC*QC
       QG = QGC*QC
       QF = QFC*QC
       QS = QSC*QC
       QR = QRC*QC
       VL = VLC*BW
       VG = VGC*BW
       VF = VFC*BW
       VS = VSC*BW
       VR = VRC*BW
       VMAX = VMAXC*BW**0.75
       KF = KFC/BW**0.25
       VK = VMAXC/KM

END     $'End of initial'

DYNAMIC

DERIVATIVE

      'CI = Concentration in inhaled air (mg/l)'
      RAI = RATS*QP*(CA/PB-CI)-(KL*AI)
       AI = INTEG(RAI,AI0)                          $ 'CHAMBER'
       CI = AI/VCH                                  $ 'WITH X RATS'
       CP = CI*24450./MW
'-------------------------------------------------'
      'CA = Concentration in arterial blood (mg/l)'
       CA = (QC*CV+QP*CI)/(QC+(QP/PB))

      'AX = Amount exhaled per rat (mg)'
       CX = CA/PB
    CXPPM = (0.7*CX+0.3*CI)*24450./MW
      RAX = QP*CX
       AX = INTEG(RAX,0.)

      'AS = Amount in slowly perfused tissues per rat (mg)'
      RAS = QS*(CA-CVS)
       AS = INTEG(RAS,0.)
      CVS = AS/(VS*PS)
       CS = AS/VS

      'AR = Amount in rapidly perfused tissues per rat (mg)'
      RAR = QR*(CA-CVR)
       AR = INTEG(RAR,0.)
      CVR = AR/(VR*PR)
       CR = AR/VR

      'AF = Amount in fat tissue per rat (mg)'
      RAF = QF*(CA-CVF)
       AF = INTEG(RAF,0.)
      CVF = AF/(VF*PF)
       CF = AF/VF

      'AG = Amount in gut tissue per rat (mg)'
      RAG = QG*(CA-CVG)
       AG = INTEG(RAG,0.)
      CVG = AG/(VG*PG)
```

```
       CG = AG/VG

      'AL = Amount in liver tissue per rat (mg)'
      RAL = QL*(CA-CVL)+QG*(CVG-CVL)-RAM
       AL = INTEG(RAL,0.)
      CVL = AL/(VL*PL)
       CL = AL/VL

      'AM = Amount metabolized per rat  (mg)'
      RAM = (VMAX*CVL)/(KM+CVL) + KF*CVL*VL  $'(mg/hr)'
       AM = INTEG(RAM,0.)                     $'Amount (mg)'

      'CV = Mixed venous blood concentration per rat (mg/l)'
       CV = (QF*CVF + (QL+QG)*CVL + QS*CVS + QR*CVR)/QC

'AMOUNT INHALED PER RAT'
       RINH = QP*CI
       AINH = INTEG(RINH,0)

'TMASS = MASS BALANCE PER RAT'
      TMASS = (AS+AR+AF+AM+AL+AX+AG)
      BAL = AINH - TMASS

TERMT (T.GE.TSTOP)

END       $'End of derivative'
END       $'End of dynamic'
END       $'End of program'
```

```
'UPTK1301.CMD'
'GAS UPTAKE DATA FOR HCFC 1301'

SET TITLE = '1301 Gas Uptake'

PREPAR T,'ALL'

SET GRDCPL=.F.    $'Turns off grid lines'

PROCED ARRAY1
SET CONCJ=121.5, 1201.5, 2992.5, 5557.
SET BWJ=.307,.326,.310,.311
SET J=1,JJ=1.0
END

PROCED CONDIT
SET KL=.041
SET PLA=.85, PGA=.69, PFA=3.95, PRA=.85
SET PSA=.59, PB=.715
SET MW=148.91
SET RATS=3, VCHC=8., SODA=.15
SET QPC=14., QCC=14.
DISPLAY QPC,QCC,VMAXC,KM,KFC,PB,PLA,PGA,PFA,PSA
END

PROCED INHAL
DATA
T         CP       JJ
0.0       .        1.0   INITIAL
0.0833    114.0    .
0.1670    113.0    .
0.2500    113.0    .
0.4170    112.0    .
0.5000    111.0    .
0.7500    109.0    .
1.0000    107.0    .
1.2500    105.0    .
1.5000    103.0    .
1.7500    101.0    .
2.0000     99.7    .
2.2500     97.8    .
2.5000     96.2    .
2.7500     95.8    .
3.0000     94.9    .
3.2500     94.3    .
3.5000     93.4    .
3.7500     92.4    .
4.0000     91.5    .
4.2500     90.4    .
4.5000     89.8    .
4.7500     88.6    .
5.0000     87.7    .
5.2500     87.2    .
5.5000     86.2    .
5.7500     85.5    .
6.0000     85.3    .
0.0          .     2.0   INITIAL
0.0833   1100.0    .
0.1670   1100.0    .
0.2500   1090.0    .
0.3330   1090.0    .
0.4170   1080.0    .
0.5000   1080.0    .
```

```
0.7500   1060.0    .
1.0000   1050.0    .
1.2500   1030.0    .
1.5000   1020.0    .
1.7500   1000.0    .
2.0000    988.0    .
2.2500    974.0    .
2.5000    962.0    .
2.7500    953.0    .
3.0000    938.0    .
3.2500    926.0    .
3.5000    910.0    .
3.7500    899.0    .
4.0000    886.0    .
4.2500    878.0    .
4.5000    868.0    .
4.7500    858.0    .
5.0000    845.0    .
5.2500    835.0    .
5.5000    824.0    .
5.7500    818.0    .
6.0000    811.0    .
0.0           .    3.0    INITIAL
0.0833   2800.0    .
0.1670   2780.0    .
0.2500   2740.0    .
0.3330   2730.0    .
0.4170   2710.0    .
0.5000   2700.0    .
0.7500   2640.0    .
1.0000   2600.0    .
1.2500   2540.0    .
1.5000   2500.0    .
1.7500   2460.0    .
2.0000   2420.0    .
2.2500   2390.0    .
2.5000   2360.0    .
2.7500   2320.0    .
3.0000   2270.0    .
3.2500   2240.0    .
3.5000   2220.0    .
3.7500   2190.0    .
4.0000   2160.0    .
4.2500   2140.0    .
4.5000   2120.0    .
4.7500   2100.0    .
5.0000   2070.0    .
5.2500   2040.0    .
5.5000   2010.0    .
5.7500   2000.0    .
6.0000   1970.0    .
0.0           .    4.0    INITIAL
0.0833   5160.0    .
0.1670   5150.0    .
0.2500   5100.0    .
0.3330   5040.0    .
0.4170   5030.0    .
0.5000   5000.0    .
0.7500   4920.0    .
1.0000   4890.0    .
1.2500   4840.0    .
1.5000   4790.0    .
1.7500   4700.0    .
2.0000   4610.0    .
```

```
2.2500   4550.0    .
2.5000   4500.0    .
2.7500   4470.0    .
3.0000   4420.0    .
3.2500   4360.0    .
3.5000   4290.0    .
3.7500   4250.0    .
4.0000   4190.0    .
4.2500   4150.0    .
4.5000   4120.0    .
4.7500   4080.0    .
5.0000   4030.0    .
5.2500   4000.0    .
5.5000   3960.0    .
5.7500   3910.0    .
6.0000   3860.0    .
END
START SMOOTH
END
```

APPENDIX B

CODES AND COMMAND FILE FOR COMPUTER SIMULATION OF CF_3I PHARMACOKINETICS

```
PROGRAM: CLOSED CHAMBER MODEL CF3I GAS-UPTAKE EXPOSURES
'Based on:'
'Template Model with Code for Gut and Liver - 30 March 1993'
'-------------------------------------------------------------'
INTEGER  J
ARRAY CONCJ(5), BWJ(5)
CONSTANT CONCJ = 111.5,648.4,1228.3,2955.6,5867.
CONSTANT BWJ = .220,.246,.228,.2366,.2385
CONSTANT J=1, JJ=1.0

INITIAL

ALGORITHM IALG = 2  $'Gear method for stiff systems'

     'Timing commands'

CONSTANT    TSTOP = 6.    $'Length of experiment (hrs)'
CONSTANT     CINT = .1    $'Communication interval'

J = INT(JJ)
CONC = CONCJ(J)
BW = BWJ(J)
CONSTANT    KL  = .027    $'FIRST ORDER CHAMBER LOSS (LN AREA CTS/HR)'
CONSTANT    BW = 0.23    $'Body weight (kg)'

CONSTANT    QPC = 14.00    $'Alveolar ventilation rate (l/hr)'
CONSTANT    QCC = 14.00    $'Cardiac output (l/hr)'

CONSTANT    QLC = .032   $'Fractional blood flow to liver'
CONSTANT    QGC = .183   $'Fractional blood flow to gut'
CONSTANT    QFC = .058   $'Fractional blood flow to fat'
CONSTANT    QSC = .255   $'Fractional blood flow to slow'
CONSTANT    QRC = .472   $'Fractional blood flow to rapid'

CONSTANT    VLC = .037   $'Fraction liver tissue'
CONSTANT    VGC = .033   $'Fraction gut tissue'
CONSTANT    VSC = .558   $'Fraction slow tissue'
CONSTANT    VRC = .031   $'Fraction rapid tissue'

VFC = .01*(35.0*BW+2.1)  $'Fraction fat tissue'

CONSTANT    PLA = 1.223    $'Liver/air partition coefficient'
CONSTANT    PGA = 1.569    $'Gut/air partition coefficient'
CONSTANT    PFA =11.237    $'Fat/air partition coefficient'
CONSTANT    PSA = 1.269    $'Slowly perfused tissue/air partition'
CONSTANT    PRA = 1.223    $'Richly perfused tissue/air partition'
CONSTANT    PB =  1.746    $'Blood/air partition coefficient'

PL=PLA/PB  $'Liver/blood partition coefficient'
PG=PGA/PB  $'Gut/blood partition coefficient'
PF=PFA/PB  $'Fat/blood partition coefficient'
PS=PSA/PB  $'Slow/blood partition coefficient'
PR=PRA/PB  $'Rich/blood partition coefficient'

CONSTANT    MW = 195.9  $'Molecular weight (g/mol)'
CONSTANT    VMAXC=0.375 $'Maximum velocity of metabolism (mg/hr-1kg)'
CONSTANT    KM = 0.1    $'Michaelis-Menten constant (mg/l)'
CONSTANT    KFC = 1.6   $'First order metabolism rate constant (/hr-1kg)'
CONSTANT    CONC=100.   $'Inhaled concentration (ppm)'
CONSTANT    RATS = 3.   $'Number of rats (for closed chamber)'
CONSTANT    VCHC = 8.0  $'Volume of closed chamber (l)'
CONSTANT    SODA = .15  $'Volume of soda lime (l)'
```

```
VCH = VCHC-(RATS*BW)-SODA    $'Net chamber volume (l)'
AI0 = CONC*VCH*MW/24450.     $'Initial amount in chamber (mg)'

     'Scaled parameters'

       QC = QCC*BW**0.75
       QP = QPC*BW**0.75
       QL = QLC*QC
       QG = QGC*QC
       QF = QFC*QC
       QS = QSC*QC
       QR = QRC*QC
       VL = VLC*BW
       VG = VGC*BW
       VF = VFC*BW
       VS = VSC*BW
       VR = VRC*BW
       VMAX = VMAXC*BW**0.75
       KF = KFC/BW**0.25
       VK = VMAXC/KM

END     $'End of initial'

DYNAMIC

DERIVATIVE

      'CI = Concentration in inhaled air (mg/l)'
      RAI = RATS*QP*(CA/PB-CI)-(KL*AI)
       AI = INTEG(RAI,AI0)                          $ 'CHAMBER'
       CI = AI/VCH                                  $ 'WITH X RATS'
       CP = CI*24450./MW
'-------------------------------------------------'
      'CA = Concentration in arterial blood (mg/l)'
       CA = (QC*CV+QP*CI)/(QC+(QP/PB))

      'AX = Amount exhaled per rat (mg)'
       CX = CA/PB
    CXPPM = (0.7*CX+0.3*CI)*24450./MW
      RAX = QP*CX
       AX = INTEG(RAX,0.)

      'AS = Amount in slowly perfused tissues per rat (mg)'
      RAS = QS*(CA-CVS)
       AS = INTEG(RAS,0.)
      CVS = AS/(VS*PS)
       CS = AS/VS

      'AR = Amount in rapidly perfused tissues per rat (mg)'
      RAR = QR*(CA-CVR)
       AR = INTEG(RAR,0.)
      CVR = AR/(VR*PR)
       CR = AR/VR

      'AF = Amount in fat tissue per rat (mg)'
      RAF = QF*(CA-CVF)
       AF = INTEG(RAF,0.)
      CVF = AF/(VF*PF)
       CF = AF/VF

      'AG = Amount in gut tissue per rat (mg)'
      RAG = QG*(CA-CVG)
       AG = INTEG(RAG,0.)
      CVG = AG/(VG*PG)
```

```
       CG = AG/VG

      'AL = Amount in liver tissue per rat (mg)'
      RAL = QL*(CA-CVL)+QG*(CVG-CVL)-RAM
       AL = INTEG(RAL,0.)
      CVL = AL/(VL*PL)
       CL = AL/VL

      'AM = Amount metabolized per rat  (mg)'
      RAM = (VMAX*CVL)/(KM+CVL) + KF*CVL*VL  $'(mg/hr)'
       AM = INTEG(RAM,0.)                     $'Amount (mg)'

      'CV = Mixed venous blood concentration per rat (mg/l)'
       CV = (QF*CVF + (QL+QG)*CVL + QS*CVS + QR*CVR)/QC

'AMOUNT INHALED PER RAT'
       RINH = QP*CI
       AINH = INTEG(RINH,0)

'TMASS = MASS BALANCE PER RAT'
      TMASS = (AS+AR+AF+AM+AL+AX+AG)
      BAL = AINH - TMASS

TERMT (T.GE.TSTOP)

END       $'End of derivative'
END       $'End of dynamic'
END       $'End of program'
```

```
'UPTKCF3I.CMD'
'GAS UPTAKE DATA FOR HCFC CF3I'

SET TITLE = 'CF3I Gas Uptake'

PREPAR T,'ALL'

SET GRDCPL=.F.    $'Turns off grid lines'

PROCED ARRAY1
SET CONCJ=111.5,648.4,1228.,2955.6,5867.
SET BWJ=.220,.246,.228,.2366,.2385
SET J=1,JJ=1.0
END

PROCED CONDIT
SET KL=.027
SET PLA=1.223, PGA=1.569, PFA=11.237, PRA=1.223
SET PSA=1.269, PB=1.746
SET MW=195.9,
SET RATS=3, VCHC=8., SODA=.15
SET QPC=14.0, QCC=14.0
DISPLAY QPC,QCC,VMAXC,KM,KFC,PB,PLA,PGA,PFA,PSA
END

PROCED INHAL
DATA
T              CP       JJ
0.0             .        1.0   INITIAL
0.083300      103.618925  .
0.167000      100.893179  .
0.250000       99.339248  .
0.333333       97.735022  .
0.417000       96.420210  .
0.500000       95.169902  .
0.750000       92.512083  .
1.000000       89.163992  .
1.250000       86.778430  .
1.500000       84.245130  .
1.750000       81.395859  .
2.000000       78.986955  .
2.250000       77.540392  .
2.500000       74.754263  .
2.750000       73.373815  .
3.000000       71.748126  .
3.250000       69.407132  .
3.500000       67.569290  .
3.750000       65.621446  .
4.000000       63.995923  .
4.250000       62.496197  .
4.500000       60.925760  .
4.750000       59.091267  .
5.000000       57.984620  .
5.250000       56.400129  .
5.500000       54.938278  .
5.750000       54.012453  .
6.000000       52.333737  .
0.0             .        2.0   INITIAL
0.083300      597.686344   .
0.167000      583.667563   .
0.250000      574.824343   .
0.333333      567.096343   .
0.417000      564.020850   .
```

```
0.500000      560.095592    .
0.750000      546.211894    .
1.000000      532.538674    .
1.250000      521.227834    .
1.500000      514.943337    .
1.750000      499.971122    .
2.000000      502.256536    .
2.250000      490.901717    .
2.500000      484.813560    .
2.750000      480.395092    .
3.000000      473.144594    .
3.250000      469.871189    .
3.500000      463.996652    .
3.750000      458.393852    .
4.000000      448.158964    .
4.250000      445.923813    .
4.500000      447.383023    .
4.750000      440.391696    .
5.000000      437.407305    .
5.250000      434.631822    .
5.500000      418.682612    .
5.750000      422.311002    .
6.000000      415.170456    .
0.0             .           3.0   INITIAL
0.083300   1128.735825      .
0.167000   1108.785948      .
0.250000   1096.012783      .
0.333333   1086.036758      .
0.417000   1075.252672      .
0.500000   1069.827755      .
0.750000   1050.701084      .
1.000000   1031.213056      .
1.250000   1018.777892      .
1.500000    998.491190      .
1.750000    983.193834      .
2.000000    967.493893      .
2.250000    952.985468      .
2.500000    946.712079      .
2.750000    941.000634      .
3.000000    934.461078      .
3.250000    925.916938      .
3.500000    915.480190      .
3.750000    913.949144      .
4.000000    906.032083      .
4.250000    896.361047      .
4.500000    885.759946      .
4.750000    859.197012      .
5.000000    853.643134      .
5.250000    846.718838      .
5.500000    842.380954      .
5.750000    831.830346      .
6.000000    825.111320      .
0.0             .           4.0   INITIAL
0.083300   2714.920102      .
0.167000   2674.022448      .
0.250000   2626.639409      .
0.333333   2611.217313      .
0.417000   2578.882104      .
0.500000   2562.493075      .
0.750000   2503.364635      .
1.000000   2470.860938      .
1.250000   2430.675022      .
1.500000   2407.075891      .
1.750000   2371.307122      .
```

```
2.000000   2337.673807   .
2.250000   2304.666532   .
2.500000   2284.377282   .
2.750000   2266.535068   .
3.000000   2245.370951   .
3.250000   2214.153879   .
3.500000   2195.832079   .
3.750000   2171.075919   .
4.000000   2149.864808   .
4.250000   2134.025118   .
4.500000   2111.121762   .
4.750000   2100.349590   .
5.000000   2074.380379   .
5.250000   2058.847468   .
5.500000   2040.898265   .
5.750000   2015.584043   .
6.000000   1997.317869   .
0.0                .     5.0   INITIAL
0.083300    5508.230988  .
0.167000    5378.203854  .
0.250000    5261.385353  .
0.333333    5215.735645  .
0.417000    5143.595303  .
0.500000    5086.184354  .
0.750000    4891.626035  .
1.000000    4768.083955  .
1.250000    4669.155694  .
1.500000    4552.126697  .
1.750000    4480.472278  .
2.000000    4406.280024  .
2.250000    4352.254110  .
2.500000    4297.984213  .
2.750000    4230.026588  .
3.000000    4183.106058  .
3.250000    4158.387759  .
3.500000    4081.340804  .
3.750000    4032.043993  .
4.000000    3970.043260  .
4.250000    3929.224949  .
4.500000    3885.317569  .
4.750000    3818.980663  .
5.000000    3801.775991  .
5.250000    3750.540150  .
5.500000    3723.417954  .
5.750000    3669.359219  .
6.000000    3635.394650  .
END
START SMOOTH
END
```